pensated biliary cirrhosis. *Methods:* Using a previously described model of hepatic decompensation (IL-6-/-mice 12 weeks after bile duct ligation (BDL), we analyzed the expression of cell cycle proteins and mRNA. Reactive oxygen species (ROS) were examined by analysis of nitrotyrosine as a mechanism of mito-inhibition. We illustrated the influence of p21 by analyzing hepatocyte proliferation following BDL in p21-/- mice. *Results:* A significantly lower hepatic mass was associated with a significantly reduced number of dividing hepatocytes in decompensated cirrhosis compared to compensated cirrhosis. Expression of G1 cyclins (D and E) and cyclin dependent kinases (cdk2/4/6) were similar in both groups. However, the S phase cyclin A was significantly lower in decompensated cirrhosis reflecting the decreased hepatocyte proliferation and suggesting that cell cycle cessation occurs prior to S phase. The cyclin dependent kinase inhibitor p21 can act to prevent cell cycle progression at G1/S phase, therefore we examined the expression of this mito-inhibitor in our model. Significantly higher expression of p21 was observed in liver lysates and localized to hepatocyte nuclei of decompensated livers. Elevated p21 has been attributed to increased stress by ROS. We examined the production of ROS by measuring nitrotyrosine residues. ELISA analysis of liver lysates revealed significantly higher nitrotyrosine after BDL in decompensated liver. To illustrate the influence of p21 on hepatocyte proliferation and liver mass, we subjected p21-/- mice to 12 weeks BDL. P21-/- mice had a significantly higher liver mass index along with significant increases in hepatocyte mitosis compared to similarly treated wild-type mice. *Conclusion:* Decompensation during biliary cirrhosis shows diminished hepatic mass and reduced hepatocyte proliferation associated with elevations in ROS, elevated heopatocyte p21 expression, and lower S phase cyclin A expression. These findings provide insight to the mechanisms associated with hepatic decompensation.

The following authors have indicated they have no relationships to disclose:

John G Lunz, III, Tsukasa Ezure, Hirokazu Tsuji, Anthony J Demetris

1262

ESTIMATED IMPACT OF RIBAVIRIN (RBV) DOSE REDUCTIONS ON SVR IN THE TREATMENT OF HCV GENOTYPE 1-INFECTED PATIENTS. *Thomas Abbott III, The MedStat Group, Philadelphia, PA; Vaibhavi Desai, Gerhard J Leitz, Samir H Mody, Ortho Biotech Clinical Affairs, LLC, Bridgewater, NJ*

Background: The standard of care for treatment of chronic HCV infection is combination therapy with pegylated interferon (PEG-IFN) and RBV. The major side effect of RBV is a dose-dependent hemolytic anemia. The traditional approach to managing this anemia has been RBV dose reduction to 600 mg/day when hemoglobin decreases to <10 g/dL. However, increasing evidence suggests that decreasing RBV dose may compromise SVR (Manns, Hadziyannis, McHutchinson). We sought to retrospectively analyze the impact of RBV dose reductions on SVR from 3 HCV treatment trials evaluating the newer regimen, PEG-IFN + RBV. *Objective:* To quantify the impact of RBV dose reductions on SVR in HCV genotype 1 patients using data from PEG-IFN + RBV registration trials published from 2001-2004.

Methods: A model was created from pooled aggregate data on SVR and RBV dose levels from Manns (2001), Fried (2002) and Hadziyannis (2004) and used to estimate a RBV dose response curve. RBV doses were decreased in response to adverse events in 9% to 44% of patients in these trials. Estimates of the distribution of final RBV dose levels were constructed for each study arm based on published information. Overall SVR was viewed as a linear combination of dose-specific response rates. Using cross study variation in study design and estimated final doses, the implied RBV dose response curve for each patient group was calculated using maximum likelihood *Methods.*

Results: Table 1 shows the estimated SVR rates in HCV genotype 1 patients when treated at various RBV doses in combination with PEG-IFN. At full RBV dose, SVR is estimated in the model to be 58% — similar to the findings from McHutchinson (2002). In this analysis, when RBV dose decreased from 1000-1200 mg/day to 800 mg/day, estimated SVR rate dropped to 44% (25% relative reduction). Further reduction of dose to 600 mg/day results in an estimated SVR rate of 28% (an additional 36% relative reduction).

Conclusion: This model shows that in HCV genotype 1 patients, RBV dose reductions have a dramatic impact on SVR. Strategies for maintaining RBV dose and improving adherence to therapy are needed in order to maximize HCV treatment success.

Table 1

RBV Treatment Outcomes	SVR
Full dosage & compliance	58%
Decreased dosage (800 mg)	44%
Decreased dosage (600 mg)	28%
Discontinuation of RBV	21%

Disclosures:

Thomas Abbott, III - Ortho Biotech Products, L.P.: Consultant/Advisor

Vaibhavi Desai - Ortho Biotech Products, L.P.: Employee

Gerhard J Leitz - Ortho Biotech Products, L.P.: Employee

Samir H Mody - Ortho Biotech Products, L.P.: Employee

1263

DIABETES INCREASES THE RISK OF HEPATOCELLULAR CARCINOMA IN THE UNITED STATES: A POPULATION BASED CASE-CONTROL STUDY. *Jessica A Davila, Robert O Morgan, Yasser Shaib, Houston Center for Quality of Care and Utilization Studies, Houston, TX; Katherine A McGlynn, Division of Cancer Epidemiology and Genetics, Bethesda, MD; Hashem B El-Serag, Houston Center for Quality of Care and Utilization Studies, Houston, TX*

Purpose: Diabetes has been associated with an increased risk of hepatocellular carcinoma (HCC) in studies of referred patients. This is the first population-based case-control study in the United States to examine this association while adjusting for other major risk factors related to HCC.

Methods: Using the newly created and validated SEER-Medicare linked data, we identified patients age 65 years and older diagnosed with HCC and randomly selected non-cancer controls between 1994-1999. Only cases and controls with continuous Medicare enrollment for 3-years prior to the index date were examined. Inpatient and outpatient claims files were searched for diagnostic codes indicative of diabetes, hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic liver disease, and hemochromatosis. HCC patients without these conditions were categorized as idiopathic. Unadjusted and adjusted odds ratios were calculated in logistic regression analyses.

Results: We identified 2,061 HCC patients and 6,183 non-cancer controls. Compared to non-cancer controls, patients with HCC were younger (76 vs. 78 years), male (66% vs. 36%), and non-white (34% vs. 18%). The proportion of HCC patients with diabetes (43%) was significantly greater than non-cancer controls (19%). In multiple logistic regression analyses that adjusted for demographics features and other HCC risk factors (HCV, HBV, alcoholic liver disease, and hemochromatosis), diabetes was associated with a 3-fold increase in the risk of HCC. In a subset of patients without these major risk factors, the adjusted odds ratio for diabetes declined but remained significant (adjusted OR = 2.87; 95% CI: 2.49-3.30). A significant positive interaction between HCV and diabetes was detected ($p<0.0001$). Similar findings persisted in analyses restricted to diabetes recorded between 2 and 3-years prior to HCC diagnosis.

Conclusions: Diabetes is associated with a 2 to 3-fold increase in the risk of HCC, regardless of the presence of other major HCC risk factors. Findings from this population-based study support a causal relationship between diabetes and HCC.

The following authors have indicated they have no relationships to disclose:

Jessica A Davila, Robert O Morgan, Yasser Shaib, Katherine A McGlynn, Hashem B El-Serag